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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,450	03/29/2002	Gilbert Gorr	STURK 0003	9421
24203 7590 01/18/2007 GRIFFIN & SZIPL, PC SUITE PH-1 2300 NINTH STREET, SOUTH ARLINGTON, VA 22204			EXAMINER KUBELIK, ANNE R	
			ART UNIT	PAPER NUMBER
			1638	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		01/18/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,450	GORR ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,17 and 19-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,17 and 19-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date. _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 13 October 2006 has been entered.

2. Claims 1-6, 17 and 19-21 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The rejection of claims 1-5 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Houba-Hérin et al (1999, Plant J. 17:615-626) in view of Reutter et al (1996, Plant Tiss. Cult. Biotechnol. 2:142-147) is withdrawn in light of the Declarations of Drs. Schwartzberg and Reski and Applicant's arguments.

5. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Houba-Hérin et al in view of Reutter et al as applied to claims 1-2, 4-5 and 17-18 above, and further in view of Nasu et al (1997, J. Ferm. Bioengin. 84:519-523) is withdrawn in light of the Declarations of Drs. Schwartzberg and Reski and Applicant's arguments.

6. Claims 1-5 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reutter et al (1996, Plant Tiss. Cult. Biotechnol. 2:142-147) in view of Raskin (2000, US Patent 6,096,546, filed 1998) is withdrawn in light of the Declaration of Dr. Reski and Applicant's arguments.

Claim Rejections - 35 USC § 112

7. Claims 1-6, 17 and 20-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the production of secreted proteins in *Physcomitrella patens* by transformation with constructs that encode signal peptides operably linked to the proteins, does not reasonably provide enablement for a method for the production of secreted proteins in other mosses or in liverworts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is modified from the rejection set forth in the Office action mailed 14 March 2006, as applied to claims 1-6 and 17. Applicant's arguments and the Declaration of Dr. Reski, both filed 13 October 2006, have been fully considered but they are not persuasive.

The claims are broadly drawn to a method for the production of proteins in any moss or liverwort species, including *Physcomitrella*, *Funaria*, *Sphagnum*, *Ceratodon*, *Marchantia* and *Sphaerocarpos*.

The instant specification, however, only provides guidance for transformation of *P. patens* with a vector encoding vascular endothelial growth factor (VEGF) operably linked to a human ER transit peptide (pg 14-27).

The instant specification fails to provide guidance for transformation of other mosses or of liverworts.

The state of the art at the time of filing was that only two other species, *Ceratodon purpureus* and *Marchantia polymorpha* had been transformed. Additionally, no reports of the transformation of other moss or liverwort species appear in the post-filing art.

The extraordinary ability of *P. patens* to be transformed by targeted homologous recombination (see Schafer, 2002, Ann. Rev. Plant Biol. 53:477-501) would lead researchers to attempt to use other mosses, especially given the advantages gene targeting has in basic research (Schafer, pg 479, paragraph 2, to pg 480, paragraph 2). The lack of reports of transformation of other moss species, even ones stating that transformation in them does not occur by homologous recombination, suggest that transformation of mosses and liverworts is not straightforward.

Further, Reski (1998, Bot. Acta 111:1-15) states that “there has been a serious delay on the use of new techniques of plant molecular biology [on moss species], and molecular analysis have concentrated on *Physcomitrella*” (pg 9, column 2, paragraph 3). It is noted that Reski is one of the instant inventors.

Lastly, none of the numerous post-filing papers Applicants and their collaborators have published touting their invention have cited any other moss or liverwort other than *Physcomitrella* (see Decker et al, 2004, Curr. Opinion in Plant Biol. 7:166-170; Schaaf et al, 2005, BMC Biotechnol. 5:30-40; Wagner, 2003, Innovations in Pharm. Technol. 3:56, 58 and 60). This suggests that the method for the production of proteins in mosses or liverwort species is not enabled in species other than *P. patens* or that reviewers of the articles do not believe it is.

As the specification does not describe the transformation of any moss or liverwort other than *P. patens* with a heterologous gene, undue trial and error experimentation would be required to develop a transformation method for the full scope of other mosses and liverworts as encompassed by the claims, if transformation is even obtainable.

Given the claim breath and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Art Unit: 1638

Applicant urges that the step of transforming mosses and liverworts is not an element of the claimed invention (response pg 10).

This is not found persuasive because the full scope of starting materials for a method must be readily available or able to be made. If the prior art does not teach how to make the full scope of starting materials, the specification must. In the instant case, transformed mosses and bryophytes are not taught in the art or the specification within the full scope of the starting materials required by the claims.

Applicant urges that The Gorr and Reski Declarations state that one of skill in the art would expect other *Physcomitrella* species to behave the same way as *P. patens* in culture, and that Gorr showed that *Funaria hygrometrica* and *Marchantia polymorpha* could be transformed (response pg 11-12; Reski Declaration ¶5-6 and 11-20).

This is not found persuasive because more than culturing is required. Further, neither the specification nor the prior art teach methods of transformation for any *Funaria*, *Sphagnum* or *Sphaerocarpos* species or for any *Physcomitrella*, *Ceratodon* or *Marchantia* species other than *P. patens*, *C. purpureus* or *M. polymorpha*, much less any protonema-forming moss or liverwort.

Applicant urges that the prior citation of prior art shows that moss and liverwort transformation is well known and predictable and mature (response pg 12 and 14; Reski Declaration ¶11-12).

This is not found persuasive because the lack of reports of the transformation of other moss or liverwort species in the pre- and post filing art suggests otherwise, especially given the extraordinary advantages shown by *Physcomitrella*.

Applicant urges that no evidence to support the assertion that the invention is not enabling for other moss and liverwort species is presented (response pg 12-13).

This is not found persuasive because the lack of post-filing reports of the transformation of other moss and liverwort species provides that support.

Applicant urges that Gorr shows how easy it is to transform *Funaria hygrometrica* and *Marchantia polymorpha* (response pg 14; Reski Declaration ¶14-20).

This is not found persuasive. *M. polymorpha* has previously been transformed. *F. hygrometrica* is only one out of the 20,000 species encompassed by the claims.

Applicant urges that every species need not be enabled (response pg 14-15).

This is not found persuasive because a representative number of species must be. Three is not a representative number out of 20,000.

Applicant urges that the specification provides abundant guidance for how to use intact plants to obtain heterologous proteins in the culture medium, describes multiple moss and liverwort species, and gives details for transforming *P. patens*, such that only routine experimentation would be needed to apply the invention to other mosses and liverworts (response pg 15-17; Reski Declaration ¶22-25).

This is not found persuasive because no guidance is provided for transformation of all the listed species; further, the listed species are only a small subset of the 20,000 bryophytes that have been described (Reski Declaration ¶5).

Applicant urges that a working example is provided (response pg 17; Reski Declaration ¶26-27).

This is not found persuasive because the single working example is only provided with the only well studied moss or liverwort.

Applicant urges that the organisms are simple and predictable, and the state of the prior art is evidenced by Reuter, Zeidler, Nasu, Rasmussen, all published more than 5 years ago, and Mulhbach; the Gorr and Reski Declarations and the literature show the transformation of bryophytes is mature and well-developed (response pg 17-18; Reski Declaration ¶28-31).

This is not found persuasive because none of the published references teach transformation of any moss or liverwort other than *P. patens*, *C. purpureus* or *M. polymorpha*, and the Gorr declaration only describes the transformation of one additional species. The lack of reports of the transformation of other moss or liverwort species in the post-filing art, even in the face of its potential use in basic research, suggests that moss and liverwort transformation is not straightforward.

Applicant urges that Mulhbach states the genetic transformation of *P. patens* can be extended to other bryophytes (response pg 18; Reski Declaration ¶30).

This is not found persuasive. That it hasn't been so extended in the 8 years since the publication of that article suggests that moss and liverwort transformation is not straightforward or that the basic transformation techniques that can be used for *P. patens* cannot be used on the vast majority of other species.

Applicant urges that the skill of those in the art is high (response pg 18-19; Reski Declaration ¶32-33).

This is not found persuasive. The art of moss and liverwort transformation is in its infancy, and the lack of publications on mosses other than *P. patens* suggests that the skill in the art has not been sufficient to overcome difficulties in the field.

Applicant urges that Zeidler and Nasu show that transformation of *Ceratodon purpureus* and *Marchantia polymorpha* is known, thus the predictability of the art is high (response pg 19; Reski Declaration ¶34-35).

This is not found persuasive. *C. purpureus* and *M. polymorpha* are only two out of 20,000 species encompassed by the claims. There is no teaching in the pre- or post-filing art of other the transformation of species other than these and *P. patens*.

Applicant urges that only routine experimentation is necessary to use other species, as shown by the transformation of *Funaria hygrometrica* by Gorr; further, transformation of plant protoplasts is not the crux of the invention (response pg 19-20; Reski Declaration ¶36-38).

This is not found persuasive because transformation procedures would need to be worked out for a broad range of mosses and liverworts. Transformation is required to produce the starting materials required by the claimed method. The lack of teaching in the pre- or post-filing art of the transformation of species other than *C. purpureus*, *M. polymorpha* and *P. patens* suggests that more than routine experimentation is required.

Applicant urges that the claims are not overbroad because protonema has specific meaning in the art and the method involves two steps (response pg 20; Reski Declaration ¶39-40).

This is not found persuasive because practicing the inventions requires transformation of a broad range of mosses and liverworts, which is not taught by the specification. Thus, claim 1 is very broad.

Applicant urges that the Wands factors favor enablement (response pg 21).

This is not found persuasive because, as can be seen from the analysis above, they do not.

Applicant urges that the Examiner's analysis was flawed because each Wands factor was considered singly, and each factor alone was deemed insufficient to establish enablement (response pg 21-22).

This is not found persuasive, as the Wands factors as a whole were considered. It is noted that Applicant considered each Wands factor singly. The rejection looked at them as a whole.

Applicant urges that transformation is not part of the claims (response pg 22).

This is not found persuasive because transformation of mosses and liverworts within the full scope of the claims is required to obtain heterologous proteins from cultured transformed protonema tissue.

Applicant urges that Genentech states that the specification must supply the novel aspects of the invention, and in Genentech no starting materials were disclosed, while here there is a working example (response pg 22).

This is not found persuasive. The instant rejection is a scope of enablement rejection; the invention is enabled for *P. patens* but not for the full scope of 20,000 mosses and liverworts. Transformation of mosses other than *C. purpureus*, *M. polymorpha* and *P. patens* is novel.

Art Unit: 1638

Applicant urges that the expert testimony of Reski was not acknowledged (response pg 23).

This is not found persuasive because The Declaration of Dr Reski was only submitted with this response, and could not be considered earlier. It is considered here.

Applicant urges that whether Gorr is a person of extraordinary skill in the art is irrelevant because he is an expert and able to provide his true opinion (response pg 24).

This is not found persuasive. The lack of reports of the transformation of other moss or liverwort species in the post-filing art appears to be more reflective of the abilities of those of ordinary skill in the art.

Applicant urges that Gorr showed that the described protocols could be applied to *Funaria hygrometrica* and *Marchantia polymorpha*, supporting the position that invention is broadly applicable (response pg 24).

This is not found persuasive because *F. hygrometrica* and *M. polymorpha* are two out of 20,000 moss and liverwort species.

See *In re Vaeck* (CAFC 1991) 20 USPQ2d 1438 at pg 1445:

In so doing we do not imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.

Claim Rejections - 35 USC § 103

8. Claims 1-5, 17 and 19-21 rejected under 35 U.S.C. 103(a) as being unpatentable over Reutter et al (1996, Plant Tiss. Cult. Biotechnol. 2:142-147) in view of Lee et al (US Patent 6,020,169, filed April 1998).

The claims are drawn to a method of isolating a heterologous protein from culture medium in which in transformed *P. patens* protonema were grown.

Reutter et al teach growth of *P. patens* protonema transformed with a nucleic acid encoding a heterologous protein (pg 143, paragraph 2-3) and that these protonema produced large amounts of the heterologous protein grown in bioreactor culture (pg 143, paragraph 3; Fig. 2-3). Reutter et al also teach that *P. patens* can be grown on inorganic medium (pg 142, paragraph 4). Reutter et al do not disclose isolation of the protein from the culture medium.

Lee et al teach isolation of biologically active heterologous protein from tobacco cells grown in suspension culture. The cells were transformed with a nucleic acid encoding Mab HC operably linked to a mammalian signal peptide (column 12, line 5, to column 19, line 67).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of producing heterologous protein in *P. patens* protonema as taught by Reutter et al, to use a signal peptide in the transformation construct and isolate the protein from media as described in Lee et al. One of ordinary skill in the art would have been motivated to do so because of the advantages of being able to isolate the protein from the medium (Lee et al, column 4, lines 34-54).

9. Claims 6 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reutter et al in view of Lee et al as applied to claims 1-5, 17 and 19-21 above, and further in view of Nasu et al (1997, J. Ferm. Bioengin. 84:519-523).

The claims are drawn to a method of isolating a heterologous protein from culture medium in which in liverwort protonema were grown.

The teachings of Reutter et al in view of Lee et al are discussed above. Reutter et al in view of Lee et al do not disclose a method of isolating a heterologous protein from culture medium in which in protonema were grown, wherein the protonema were from a liverwort.

Nasu et al teach transformation of *Marchantia polymorpha* (pg 520, left column, paragraphs 1-2). *M. polymorpha* is a photoauxotroph, and thus its growth does not require sugars, vitamins, or phytohormones.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of producing a heterologous protein in protonema tissue as taught by Reutter et al in view of Lee et al, to use liverwort protonema as described in Nasu et al. One of ordinary skill in the art would have been motivated to do so because substitution of one bryophyte for another is an obvious optimization of design parameters. Optimization of parameters is a routine practice that would be obvious for one of ordinary skill in the art to employ to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the use of *M. polymorpha* would have been obvious at the time of Applicant's invention.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

Art Unit: 1638

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

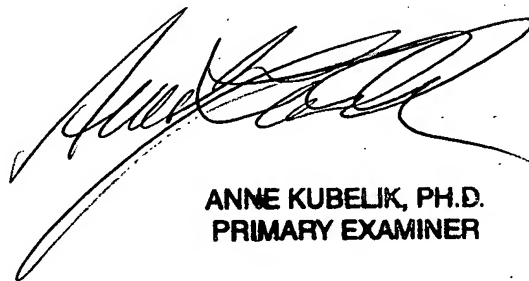
The central fax number for official correspondence is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Anne Kubelik, Ph.D.
January 8, 2007



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PRIMARY EXAMINER